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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,381	09/25/2001	Gary Lynch	1819.0040001/MAC/LBB	7154

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EXAMINER	
DOWELL, PAUL THOMAS	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,381	LYNCH ET AL.	
	Examiner	Art Unit	
	Paul Dowell	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12,14-19,36,37,59,61-68 and 70-75* is/are pending in the application.

4a) Of the above claim(s) *9-12 and 65-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,14-19,36,37,59,61-64 and 70-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 11/21/2005 is acknowledged.

Claims 1, 3-12, 14,19, 36, 37, 59, 61-68 and 70-75 are pending. Claims 9-12 and 65-68 are withdrawn; claims 1, 3-8, 14-19, 36, 37, 59, 61-64 and 70-75 are under examination in the instant office action.

Response to Arguments: Claim Objections

In the response filed 11/21/2005, Applicant's have amended the claims appropriately, therefore the objection to claims 14, 15, 63, 70 and 71 is withdrawn.

Response to Arguments: Claim Rejections - 35 USC § 112

In the response filed 11/21/2005, Applicant's have amended claims 1 and 59 to recite specific integrin antagonists, therefore the written description and enablement rejections of claims 1 and 59 under 35 USC § 112, 1st paragraph are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15 and 71 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 71 recite the limitation "wherein said antagonist is said RGD peptide, RGDS peptide, GRGDS peptide, GRGDTP peptide, GRGDSP peptide or echistatin". Claims 15 and 71 depend from claims 1 and 59, respectively. Claims 1 and 59 recite an RGDS peptide, a GRGDS peptide, a GRGDSP peptide and a GRGDTP peptide but do not recite an RGD peptide, therefore, there is insufficient antecedent basis for this limitation in claims 15 and 71. Deleting the recitation "RGD peptide" from claims 15 and 71 will overcome this rejection.

Response to Arguments: Claim Rejections - 35 USC § 102(b)

Applicant's arguments filed 11/25/2005 have been fully considered but they are not persuasive. Applicants provide no specific reasoning for the traversal of the instant 35 USC § 102(b) rejection. Applicants argue that claims 1 and 59 have been amended to refer to integrin antagonists that do not include amyloid-β. However, claims 1 and 59 have been amended to recite, "wherein said antagonist is selected from the group consisting of function blocking anti-α5 subunit integrin antibody, function blocking anti-β1 subunit integrin antibody, RGDS peptide, GRGDS peptide, GRGDSP peptide, GRGDTP peptide, echistatin and β-amyloid. Amyloid-β and β-amyloid are synonymous terms. For example, Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998) recites "amyloid-β peptide (Aβ)" in line 1 of the abstract and further recites "Aβ is a 39-42 amino acid protein derived from proteolytic cleavage of a larger membrane-spanning glycoprotein, the amyloid precursor protein (APP)" (page 1019, col. 1, paragr. 3, line 1 to col. 2, line 1). Sabo et al (Neuroscience Letters, 184:25-28, 1995) recites, "The major

core component of Alzheimer's plaques is an aggregated 40-42 amino acid peptide called β-amyloid (β/A4). The soluble monomeric peptide, derived from the larger β-amyloid precursor protein (APP)..." (page 25, col. 1, paragr. 1, lines 1-3). Matter and Sabo are referring to the same protein by various names including amyloid-β, Aβ, β/A4 or β-amyloid.

Therefore, claims 1, 3, 4, 7, 8, 16-18, 37, 59, 63, 64, 72-74 remain rejected under 35 U.S.C. 102(b) as being anticipated by Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) for reasons of record as set forth in the office action of 8/19/2005.

Response to Arguments: First Claim Rejections - 35 USC § 103(a)

Applicant's arguments filed 11/21/2005 have been fully considered but they are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues that Harris-White, even in combination with Matter, does not teach or suggest the invention of claims 1, 5, 6, 36, 59, 61 and 62. Examiner maintains that it would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by adding a substance prior to exposure to an integrin antagonist (i.e. amyloid-β) and to use the modified method to determine whether said substance is capable of inhibiting amyloid-β deposition as taught by Matter with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to use the hippocampal brain slice assay of Harris-White because the brain slice assay is more reflective of the *in vivo* situation as recognized by Harris-White (page 10368, col. 1, parag. 1, lines 2-10).

Therefore, claims 1, 5, 6, 36, 59, 61, 62 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998) for reasons of record as set forth in the office action of 8/19/2005.

Response to Arguments: Second Claim Rejections - 35 USC § 103(a)

Applicant's arguments filed 11/21/2005 have been fully considered but they are not persuasive. Applicant argues that "Matter did not determine whether DNA encoding integrin α5 ("the substance" according to the examiner's analysis) had an effect on any of amyloid-β's, anti-integrin α5 antibody's or the GRGDSP peptide's (the antagonist's) ability to induced *(sic)* sequestration, uptake or accumulation of amyloid". This argument

is not persuasive because Matter does teach, for example, that upon exposing untransfected cultures of IMR-32 cells to amyloid-β said cultures exhibit Aβ (i.e. amyloid-β) matrix deposition. Thus, upon exposure to an integrin antagonist, in the instant case said integrin antagonist being amyloid-β, said cultures exhibit amyloid-β matrix deposition (see Figure 5). Next, Matter determines the effect of a substance (i.e. DNA encoding integrin α5) on amyloid-β matrix deposition. Specifically, Matter transfects said cultures with DNA encoding integrin α5 (the substance), exposes the transfected cultures to amyloid-β (the integrin antagonist) and observes the effect of said substance to be decreased amyloid-β matrix deposition (see Figure 5). Matter further teaches that adding an anti-α5 antibody (another integrin antagonist) neutralized the effect of the DNA encoding integrin α5 (i.e. increased amyloid-β matrix deposition; see Figure 5).

Ultimately, Matter concludes that, "The α5β1 integrin may play a role in the rapid clearance of Aβ that occurs in the normal brain" (page 1027, col. 1, paragr. 1, lines 1-2), "clearance of soluble Aβ can be mediated by the α5β1 integrin" (page 1027, col. 2, paragr. 1, lines 14-15) and "Our results suggest that α5β1 integrin may mediate the clearance of Aβ, and that α5β1 may play a significant role in protecting the brain from the Aβ-initiated pathology that in its extreme form causes AD" (page 1029, col. 1, paragr. 1, lines 10-13). Thus, it would have been clear to an artisan of ordinary skill at the time of the invention that integrin antagonists would inhibit the clearance of Aβ, thereby promoting accumulation of Aβ for example, and that utilizing said integrin antagonists in an *in vitro* system would allow one to screen substances for effects of said substances on said integrin antagonist-induced accumulation of Aβ.

Therefore, claims 1, 14, 15, 59, 70, 71 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998) for reasons of record as set forth in the office action of 8/19/2005.

Response to Arguments: Third Claim Rejections - 35 USC § 103(a)

Applicant's arguments filed 11/21/2005 have been fully considered but they are not persuasive. Applicants argue that claims 1 and 59 have been amended to refer to integrin antagonists that do not include amyloid-β. However, claims 1 and 59 have been amended to recite, "wherein said antagonist is selected from the group consisting of function blocking anti-α5 subunit integrin antibody, function blocking anti-β1 subunit integrin antibody, RGDS peptide, GRGDS peptide, GRGDSP peptide, GRGDTP peptide, echistatin and β-amyloid. Amyloid-β and β-amyloid are synonymous terms. For example, Matter et al (The Journal of Cell Biology, 141:1019-1030, 1998) recites "amyloid-β peptide (Aβ)" in line 1 of the abstract and further recites "Aβ is a 39-42 amino acid protein derived from proteolytic cleavage of a larger membrane-spanning glycoprotein, the amyloid precursor protein (APP)" (page 1019, col. 1, paragr. 3, line 1 to col. 2, line 1). Sabo et al (Neuroscience Letters, 184:25-28, 1995) recites, "The major core component of Alzheimer's plaques is an aggregated 40-42 amino acid peptide called β-amyloid (β/A4). The soluble monomeric peptide, derived from the larger β-amyloid precursor protein (APP)..." (page 25, col. 1, paragr. 1, lines 1-3). Matter and

Sabo are referring to the same protein by various names including amyloid-β, Aβ, β/A4 or β-amyloid.

Further, Applicant argues that Hass does not cure the deficiencies of Harris-White. Examiner maintains that it would have been obvious to an artisan of ordinary skill at the time of the invention to modify the hippocampal brain slice method of Harris-White by substituting brain slices containing cells that are apoE deficient or apoE4 expressing with a reasonable expectation of success. An artisan of ordinary skill would have been motivated to examine the effect of apoE deficiency or apoE4 overexpression on amyloid-β deposition because of the known protein-protein interaction between apoE and amyloid-β and because of the known genetic link between apoE and Alzheimer's disease as taught by Hass et al; and to use the hippocampal brain slice assay of Harris-White because the brain slice assay is more reflective of the *in vivo* situation as recognized by Harris-White (page 10368, col. 1, parag. 1, lines 2-10).

Therefore, claims 1, 19, 59, 75 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Harris-White et al (The Journal of Neuroscience, 18:10366-10374, 1998) as evidenced by Sabo et al (Neuroscience Letters, 184:25-28, 1995) in view of Hass et al (The Journal of Biological Chemistry, 273:13892-13897, 1998) for reasons of record as set forth in the office action of 8/19/2005.

Conclusions

No claims are allowed.

Applicant's amendment necessitated the new grounds of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 7O6.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Dowell whose telephone number is 571-272-5540. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Paul Dowell
Art Unit 1632